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Chapter 14

α -ANIONS

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INTRODUCTION

Although the α -position of saturated fatty acids and esters is the most reactive site in the chain, it has shown surprising resistance to direct substitutions by many reagents. Until recent years, there have been few direct reactions of any importance for preparative purposes. Among the more prominent successes have been: halogenation (1) and sulfonation (2), which proceed in acidic media; the Claisen condensation (3), a base-induced conversion of esters to β -ketoesters; and α -alkylation of carboxylic acids by free radical addition of the acid to olefins (4). Generally, α -methylene substituted derivatives have been prepared indirectly, either through displacement of an α -halogen substituent (1) or in multistep syntheses from simpler intermediate noncarboxylic acid components. Both of these approaches suffer severe limitations in scope, convenience, and yields. To the list of successful and direct reactions of the α -methylene group now must be added the syntheses carried out with α -anions. The inherent high reactivity of carbanions has led to numerous successes.

Although the versatility of carbanions in reactions with electrophilic reagents had long provided the key to effective substitutions, a stabilized species of carboxylic acids and esters has been difficult to attain. In the Claisen condensation, the ester proceeds through a carbanion intermediate but is consumed by self-condensation. The synthetic utility of the α -carbanion has thus depended on its quantitative formation and stabilization.

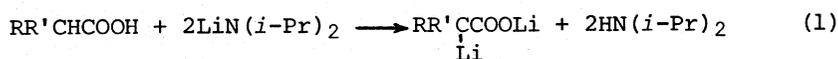
A major difficulty formerly experienced in proton abstraction from the α -methylene has been the relatively low acidity and the putative requirement for strong base. In a typical series of carbonyl-containing compounds, the order of diminishing relative acidity (pK_a units in brackets) of the α -methylene hydrogen atoms (5) is observed to be acetoacetic ester [11] > malonic ester [13] > ketone [20] > ester [24] > carboxylate salt > amide [25]. The acidity of the

α -methylene proton in carboxylate salts and esters is 12 powers lower than in acetoacetic and malonic esters, which accounts for the ease of proton abstraction from the latter pair of esters and their wide utility in synthesis. Aliphatic monobasic and dibasic esters and araliphatic esters have been examined with a variety of bases for introducing acyl and alkyl groups (3,6,7) with varying degrees of conversions. The bases commonly used in these reactions were metal alkoxides, sodium hydride, sodamide, sodium triphenylmethyl, and mesityl magnesium bromide.

APPROACHES TO THE GENERATION OF STABLE α -ANIONS

Substantial formation of intermediate α -carbanions was demonstrated by Morton *et al.* (8) in the reaction of phenylsodium with sodium phenylacetate and sodium hexanoate. By carbonation of the carbanions, they obtained the corresponding phenylmalonic (60%) and butylmalonic (17%) acids. Sodium (potassium) amide in liquid ammonia was later used for α -metalation of sodium phenylacetate (9). Sodamide (10) or sodium metal (11) at 200°C metalated sodium acetate. High temperature sodiations of propionic, n-butyric, and isobutyric acids were unsuccessful owing to decomposition of the α -sodiosalts at the temperature required for their formation. Sodium acetate was more simply metalated with sodium isopropoxide, and the resultant dianion was alkylated with mono- and dihalides. Longer chain acids were not examined (12).

The important contribution to formation of a stable dianion was provided by Creger (13) who applied lithium diisopropylamide as base for preparation of the α -lithio lithium salts from isobutyric and 2-methylbutyric acids (eq. 1). Alkylation of the dianions 1 with alkyl halides gave high



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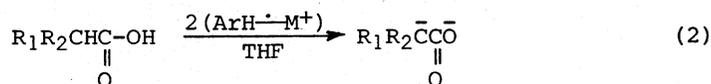
yields of trialkyl acetic acids. Creger then extended the dianion to reaction with steroidal epoxides to produce γ -lactones via cyclization of the initial γ -hydroxy carboxylic acid product (13).

Pfeffer and Silbert (14,15) studied the dilithiation reaction in detail when they experienced low alkylation yields with straight chain and longer, branched chain acids. Conversions were low because of the insolubility of the lithium dianions of straight chain acids in tetrahydrofuran. Conversions were much better when the dianions were solubil-

ized by the inclusion of hexamethylphosphoramide (HMPA). The dilithiated dianions are colloidal, aggregated structures in tetrahydrofuran having high degrees of polymerization ($n = 65-250$) (16). α -Branched acids formed dianions at slightly elevated temperature (50°C) without the need of HMPA. Conversions to dianions of both acid series were 95% as analytically determined by deuteration and carbonation. An alternative HMPA modification in toluene solution had also been reported but had been applied only to pentanoic acid, for which yields were fair (17).

Creger (18) extended his method by using mixed sodium-lithium dications for the alkylation of short and moderate straight chain acids and of branched acids unsubstituted at the α -position. Pfeffer *et al.* (15) examined the advantages of such mixed cations. Although the sodium and potassium salts of nonanoic acid were insoluble and low levels of dianions were generated, the dynamic process of dianion formation-alkylation proceeded rapidly with quantitative formation of product. Addition of HMPA was avoided, since it induced dehydrohalogenation of the alkyl halide.

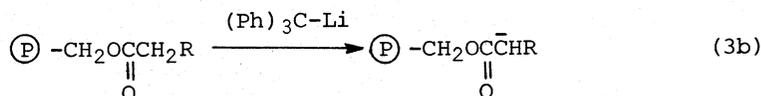
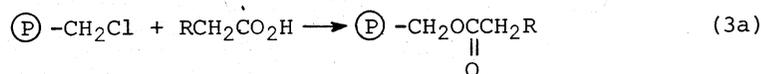
An alternative metalation of carboxylic acids by metals (Li, Na, K) dissolved in aromatic hydrocarbons ($\text{ArH} = \text{naphthalene, phenanthrene, biphenyl, etc.}$) generated dianions that added to carbonyl compounds to give β -hydroxy acids (37-80% yields) (eq. 2) (19).



Straight chain alkyl esters for which the α -anion was generated with common bases (trityl sodium, potassium hydroxide, or sodamide) gave poor yields of alkylation products (20). Claisen condensation of the ester was undoubtedly an interfering coreaction. Protection of the carboxyl group by a hindering alcohol moiety, as in *t*-butyl ester, suppressed nucleophilic attack at the carbonyl.

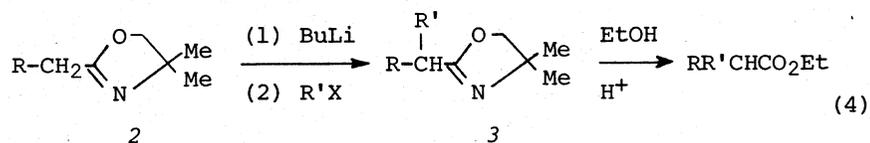
Rathke and Lindert (21) demonstrated that the tendency of esters to self-condense during ester enolate generation could be prevented at low temperature (-78°C) using the stronger base, lithium isopropylcyclohexylamide. This method has extensive applications for esters. Esters require only one mole of alkali metal compound compared to the two required for free acids.

A procedure of anchoring the carboxylic acid substrate onto a polymer to produce pendant ester groups and generating the enolate from the bound species (eq. 3) was devised by Patchornik and Kraus (22-24). The pendant esters were



prepared by reaction of the enolyzable acid with chloromethylated polystyrene (2% divinylbenzene) and removal of excess chloromethyl groups by treatment with alkyl mercaptans. The reaction involved swelling the polymeric ester in toluene containing 20% 1,2-dimethoxyethane, converting the anchored substrate to enolate with trityllithium in tetrahydrofuran (THF) at 0°C, and treating the enolate with the chosen reactant. Hydrolysis released the final product from the polymeric support. Self-condensation of the pendant ester groups does not occur at low concentration.

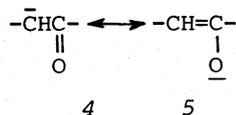
Meyers and coworkers (25) have devised an ingenious method for masking the carboxylate function as an oxazoline derivative 2. Metalation of 2 with n-butyllithium and subsequent alkylation lead to branched chain 2-alkyloxazolines



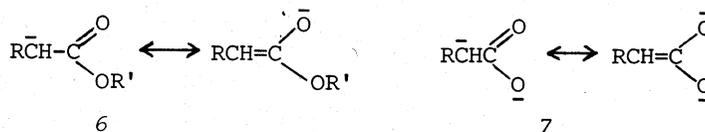
3. These products undergo facile alcoholysis to the corresponding α -substituted ester. Although this procedure requires an extra step in which to prepare the oxazoline, it eliminates the problems associated with ester self-condensations and the need for generation of an amide base.

STRUCTURE

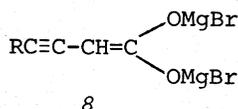
Carbanions generated by α -hydrogen abstraction from carbonyl compounds have ambident properties since they are resonance hybrids of two canonical structures, the α -carbanion 4 and the enolate anion 5. Similarly, the carboxylate



esters 6 and salts 7 may be represented in enolate forms.

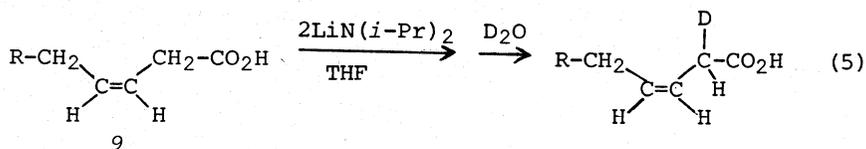


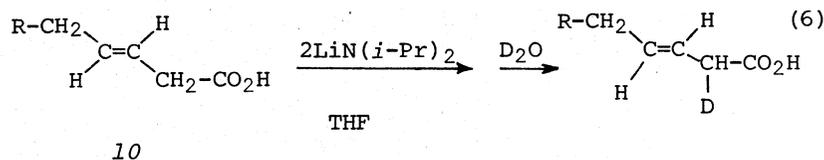
Ivanoff *et al.* (26) supported the enolate structures on the basis of infrared spectroscopic evidence on the dimagnesium bromide salts of 3-hexynoic acid and 4-phenyl-3-hexynoic acid. Displacement observed in the carbon-carbon triple bond frequency from 2260 cm^{-1} for free acid to 2190 cm^{-1} for dianion was attributed to the conjugated yne-enolate structure 8. Infrared spectra by Křiž and Schmidt (27) on a



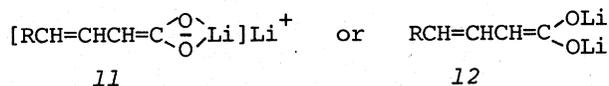
series of ester enolates show a band distinctive for enolate carbonyl at 1655 to 1678 cm^{-1} that shifts in accordance with structure. From quantum mechanical calculations, the magnitude of the shift indicates the degree of ionic character of the C-Li bond, which is a strongly polarized covalent linkage. This description excludes the possibility of complete delocalization by conjugation between α -carbon and carbonyl in free anion or ion pair structures. Conclusions on the carboxylate enolate structure were also drawn from proton and lithium-7 nmr examination of dilithio 2-methyl-3-phenylpropionate which further suggested lithium association at the oxygen sites (28).

Several chemical investigations substantiate the proposed enolate structure. Pfeffer and Silbert (16) lithiated the isomeric β,γ -alkenoic acids 9 and 10 to dianions which were subsequently quenched with deuterium oxide (eq. 5 and 6).

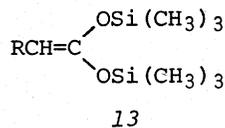




Examination of the resulting acids demonstrated quantitative incorporation of one deuterium in the α -position as well as the retention of positional and stereochemical integrity of the double bonds. These results suggest that the carbanion generated at the α -position is completely localized on oxygen in accord with the "aci-carboxylate" structures 11 or 12 and is, therefore, unable to interact as a normal delocalized allylic carbanion.



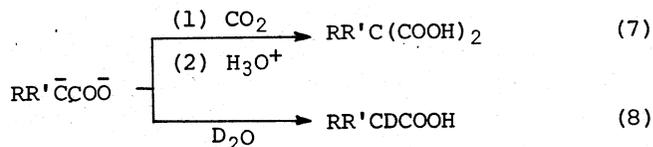
Kruger and Rochow (29) entrapped the enolate of ethyl acetate with trimethylchlorosilane (TMCS), which silylated at the C- and O- sites. Enolates of malonic esters (30-32) and monobasic acids silylated exclusively at oxygen to give rise to the bis-silyl ketene acetal structure 13. The silylated enolates undergo reactions similar to the enolates themselves.



α -SUBSTITUTIONS

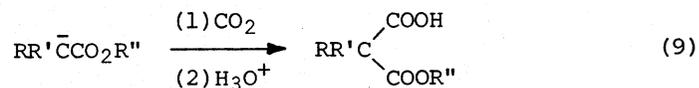
CARBONATION AND DEUTERATION

The quenching of carboxylate or ester enolates with CO_2 or D_2O is often diagnostic for their detection or quantitative measurement (eq. 7 and 8) (15). Treatment of α -anions with D_2O readily incorporates deuterium in high conversions (15). Dideuteration of the α -position is attainable by several successive metalations and D_2O quenchings.



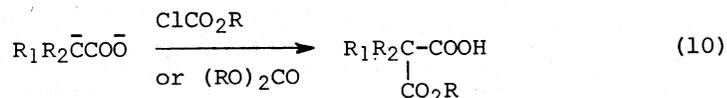
Some exceptions to the quantitative deuterium quenching of α -anions have been reported. Creger (33) has made the observation that dianions derived from toluic acids and lithium diisopropylamide appear to be intimately complexed with the generated diisopropylamine, since D_2O quenching of these species shows little or no deuterium incorporation. This implies that reprotonation occurs through the reversible transfer of the initially bonded proton held by nitrogen. In experiments utilizing deuterated diisopropylamine, Pfeffer *et al.* (15) observed that extensive deuterium exchange takes place at the carbanion center during the course of the reaction. Rathke and Lindert (21) noted that although quantitative ester enolate formation could be proven experimentally, deuterium quenching experiments gave only 50% of the anticipated incorporation. A rationale similar to Creger's was suggested to explain these results.

Carbonation of dianions offers a convenient preparation of mono- and dialkyl malonic acid (ester) synthesis (15). Ester enolates produce the monoester of malonic acids (eq. 9) (34). In cases of high temperature sodiation of sodium



acetate and sodium isobutyrate, carbonation was found to be less than quantitative owing to appreciable α -anion decomposition (10,11).

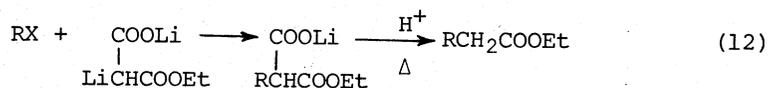
An alternative course to malonic esters through enolates involves acylation with ethyl chloroformate or alternatively with dimethyl or diethyl carbonate (35) (eq. 10).



ALKYLATION

Di- and tri-alkylacetic acids are routinely prepared in the laboratory through alkylation of stable α -anions. The α -anion reaction represents an exceptional advance over free radical addition to olefins (4) and over less direct syntheses (36,37).

Acetic acid (15) or ester (21) (eq. 11) or monoethyl malonate (38) (eq. 12) may serve in this reaction as a synthon (39) by conversion to a carbanion to provide a two-carbon homologation of acids or esters. Enolates of hindered



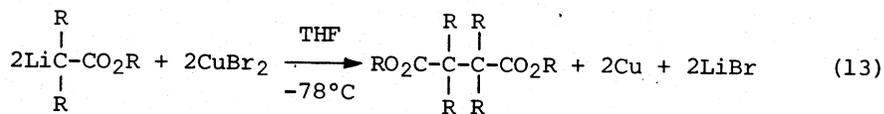
alcohol-derived esters prepared with lithium or sodamide in ammonia were alkylated with alkyl halide or dihaloalkanes to monobasic (40,41) and dibasic (41) acids, respectively.

Half acid esters of dibasic acids are preferentially alkylated at the methylene adjacent to the ester, which reflects its higher acidity relative to α -methylene in the carboxylate salt (42). Polymer-pendant esters that were described earlier have also been a source of α -branched acids (24).

The most facile method of preparation of di- and tri-alkylacetic acids is through alkylation of carboxylate enolates prepared with lithium diisopropylamide (13-15,18). Straight chain acids were nearly quantitatively alkylated in tetrahydrofuran solution containing one equivalent HMPA compared to less than 50% conversions in the absence of HMPA (15). The extremes of the common members in the homologous series, lithium acetate and lithium octadecanoate, were insoluble in tetrahydrofuran but dissolved and alkylated in 2-3 equivalents of the cosolvent. The effect of mixed alkali cations on alkylation has been discussed earlier.

Simple branched chain acids or esters, illustrated by isobutyric acid and methyl isobutyrate, can be metalated with lithium diisopropylamide and alkylated to the corresponding trialkylacetic acids in high conversion (13). However, as the alkyl branching of the substrate acid increased in length, yields of trialkylacetic acid rapidly declined (15). The steric interference of the longer chains inhibited dianion formation at room temperature. Elevation to higher temperature (50°C) accelerated proton abstraction of the branched chain acids, leading to routine and nearly quantitative alkylation of the substrate acid.

An interesting approach to substituted succinic acids was devised by Rathke and Lindert (43), who dimerized ester enolates of monobasic acids with copper bromide promoter (eq. 13).

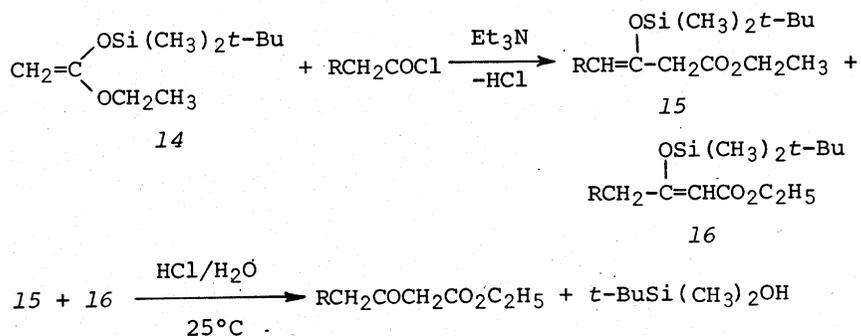


ACYLATION

β -Keto esters, β -keto acids, and ketones are prepared by acylation of α -anions, the ketones arising via decarboxylation of the former two compounds. The characteristic self-condensation of esters, as in the acylation of ester enolates by esters in the Claisen condensation to make β -keto esters (3), is not shared by carboxylate salts.

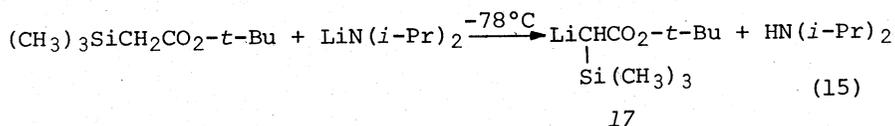
For preparation of ketones via α -anions, the use of acyl chlorides as acylating agents and carboxylate salts for enolate generation are generally superior to esters. β -Keto esters were prepared by acyl chloride acylation of sodium enolates of α - and β -substituted esters (44) and lithium enolates of unbranched and α -branched esters (45-47). The enolates of α, α -disubstituted esters and, surprisingly, the enolates with β -carbon branching resist self-condensation at moderate temperatures because of steric crowding about the carboxyl group (48). Angelo (19) utilized alkali metal radical anions for dianion generation from carboxylic acids that he acylated with esters. Acyl chloride acylation of carboxylate dianions generated by lithium diisopropylamide is an effective synthetic route to highly substituted ketones (49). The latter method is convenient for isolation of the β -keto acids as their diisopropylammonium salts which allow purification without decomposition. The β -keto acids have also been isolated as trimethylsilyl esters ($\text{RCOCR}_1\text{R}_2\text{CO}_2\text{SiMe}_3$) (32).

Rathke and Sullivan (50) have innovatively applied silylated enolates of ethyl acetate to these condensations. The O-silyl ketene acetal **14** reacted with acyl chloride in the presence of triethylamine to give a mixture of two isomeric silylated enolic keto esters **15** and **16** that hydrolyzed to the β -keto esters (Scheme 1). O-Silyl ketene acetal with a single α substitution undergoes reaction, but the method is

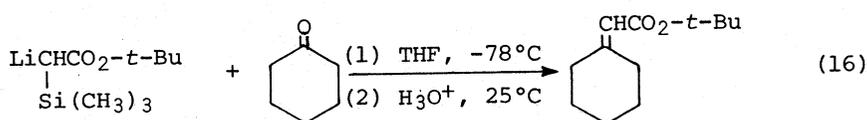


Scheme 1

Rathke *et al.* (57) have made use of a silylated *t*-butyl acetate in the form of its lithium ester enolate 17 (eq. 15).

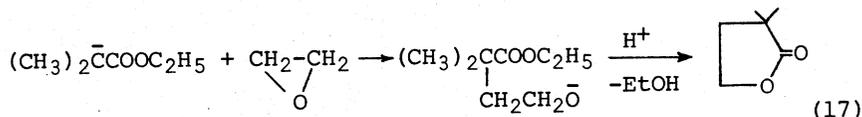


By virtue of the silylation, the derived structure is in effect an incipient dianion of the ester. Addition of an aldehyde or ketone, shown in eq. 16 with cyclohexanone, formed the adduct which hydrolyzed and dehydrated to the α,β -unsaturated ester. The utility of the reaction with longer chain esters was not examined.



EPOXIDE ADDITION

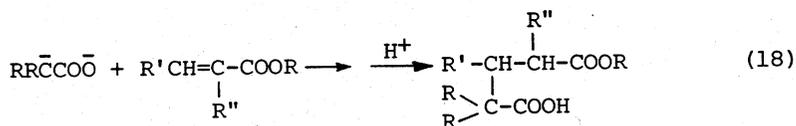
α -Lactones are prepared by nucleophilic addition of enolates to epoxides. Hudson and Hauser (44) prepared α,α -dimethylbutyric lactone by ethoxylation of ethyl isobutyrate enolate (eq. 17). The preparation of spirolactones was



realized by Creger (13,58) through the reaction of α -anions generated with lithium diisopropylamide.

MICHAEL ADDITION

Michael addition of enolates to α,β -unsaturated esters is a method of preparation of substituted glutaric acid derivatives (32) (eq. 18). Methyl acrylate is subject to



addition at -78°C but polymerizes anionically at room temperature. Acrylonitrile and crotonitrile polymerize in the presence of isobutyrate dianion even at -78°C but cinnamo-

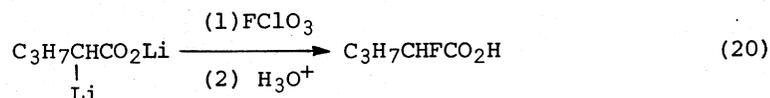
nitrile yields the expected Michael adduct.

HALOGENATION

Fluorination. Direct α -fluorination of acids and esters has been difficult to effect in practice. The active malonic ester enolate reacted with perchloryl fluoride with formation of difluoromalonic esters and side-products (59,60). The second fluorine insertion arises through proton-cation exchange between malonic ester enolate and the monofluoromalonic ester (eq. 19), followed by fluorination of the monofluoromalonate enolate. The analogous preparation of α -



fluoro fatty acid in high yield was obtained from α -alkyl malonic ester by a carefully controlled enolate reaction in toluene (61). Direct synthesis of α -fluoro acids from carboxylic acids had limited success in the reaction of perchloryl fluoride with butyrate dianion (eq. 20) (17).

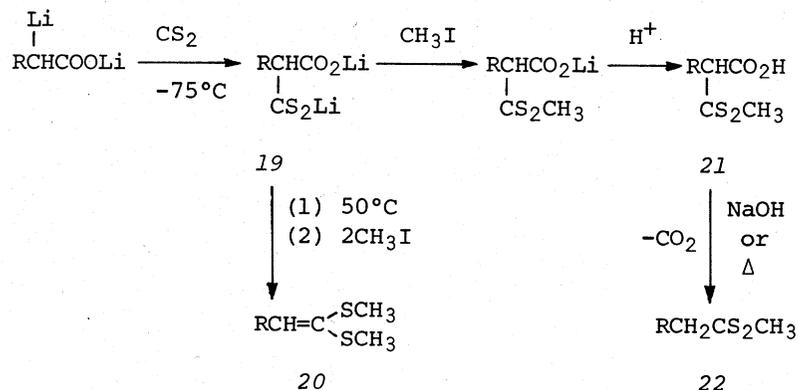


Bromination and Iodination. The time honored Hell-Volhard-Zelinski reaction for derivation of α -halo carboxylates may now be superseded by direct halogenation of α -anions. Lithium ester enolates have given high yields of α -bromo and α -iodo esters by reverse addition of ester enolates to the halogen solution at -78°C (62). Direct addition of halogen to enolate solution should be avoided to prevent dimerization to succinic ester.

SUBSTITUTIVE DECARBOXYLATIONS

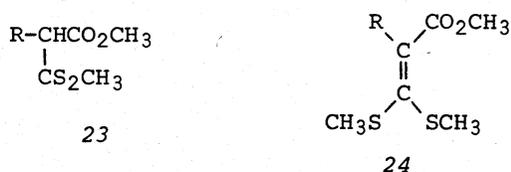
Substitution by a strong electronegative or highly polarizable functionality is accompanied by decarboxylation. The reaction in effect assumes the characteristics of a carboxyl displacement in which the carboxyl serves as the "leaving group." It thus complements other decarboxylations, for example, the Hunsdiecker Reaction (63,64), by extending the scope of substituents that may be incorporated in place of the carbonyl. It differs mechanistically from the Hunsdiecker by involving substitution at the adjacent carbon followed by decarboxylation whereas the Hunsdiecker proceeds through formation of an intermediate acyloxy derivative (RCOOX) followed by decarboxylative substitution.

dithioester 22 (Scheme 4). In a similar sequence with ester



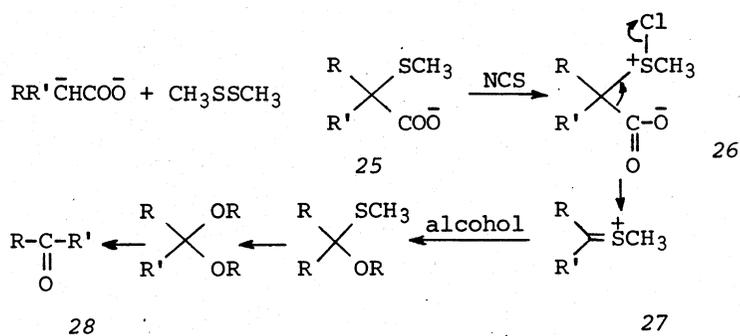
Scheme 4

enolate, carbon disulfide leads to 23 and 24 as products. The derivatives 21, 23, and 24 are the first reported example of carboxylated derivatives of dithioesters and ketene mercaptals.



OXIDATIVE DECARBOXYLATION

Trost and Tamaru (68,69) have devised a unique method



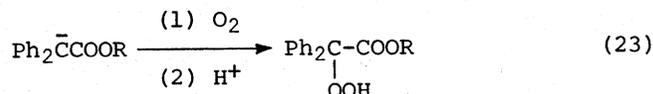
Scheme 5

for preparing ketones from carboxylic acids through the agency of a methylthio substituent. Sulfenylation of dianion of dialkylated carboxylic acid with dimethyl disulfide proceeded nearly quantitatively to 25 (Scheme 5). In a mixture of sodium bicarbonate and N-chlorosuccinimide (NCS) in alcohol, the tendency of sulfides to form chlorosulfonium salts 26 induced decarboxylation to form the alkyl thiononium ion 27 that progressed to ketone 28 through alcoholysis and hydrolysis.

HETEROATOM SUBSTITUTIONS

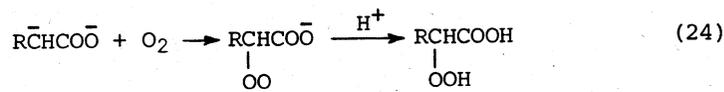
AUTOOXIDATION: α -HYDROPEROXIDE AND α -HYDROXIDE

The resistance of α -methylene to direct oxygenation has been overcome through the high reactivity of α -anions. The first α -hydroperoxy esters were reported for autoxidation of diaryl acetic esters in pyridine solution of benzyltrimethylammonium hydroxide (70) (eq. 23). The aliphatic species, *t*-butyl 2-hydroperoxyisobutyrate and ethyl α -hydroperoxy-cyclohexanecarboxylate, were later prepared using potassium *t*-butoxide in dimethyl sulfoxide (71). Adam and Liu (72)



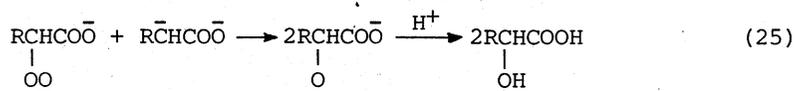
reported that photodecarboxylation of di-*n*-butylmalonylperoxide in the presence of hydrogen peroxide gave 2-butyl-2-hydroperoxyhexanoic acid, but the product resisted purification. Their alternative successful approach involved oxygenation of the silylated derivative of the enolate dianion of 3,3-dimethylbutyric acid.

α -Hydroperoxides were prepared directly from the carboxylate dianions and ester enolates of straight chain and α -branched chain acids by Konen *et al.* (73) (eq. 24).

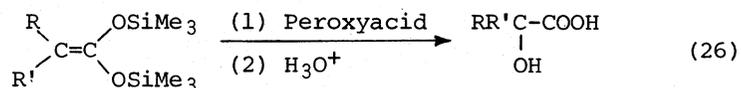


Oxygenation of the α -anions in ethyl ether at -78°C gave products in moderate to high yields that were readily purified.

Oxygenation of dianions at ambient temperature leads to high conversions of α -hydroxy acids (73). The reaction proceeds through oxidation-reduction between α -peroxyanion and α -anion (eq. 25).

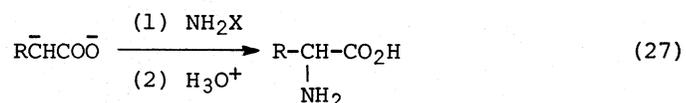


The same reaction carried out with air as the oxidant yields α -hydroxy acids in diminished yields (74). α -Hydroxy acids were also derived in high yields by peroxyacid oxidation of the silylated enolate, ketene bis-(trimethylsilyl) acetal (eq. 26) (75).



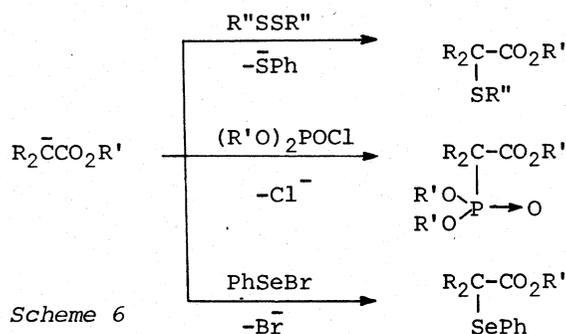
AMINATION

The first direct synthesis of an α -amino acid was obtained by amination of a carboxylate dianion (76) (eq. 27). Of several NH_2X reagents studied, *O*-alkylhydroxylamines ($\text{X} = \text{-OR}$) were the most effective.



INSERTION OF S, P, Se

Trost and Tamaru (68,69) sulfenylated carboxylate dianions with dimethyl disulfide (Scheme 6: $\text{R}' = \text{Li}$; $\text{R}'' = \text{CH}_3$). The reaction was alternatively carried out by Brocksom *et al.* (76) on ester enolates (Scheme 6: $\text{R}' = \text{alkyl}$; $\text{R}'' = \text{Ph}$). The latter workers also succeeded in the incorporation of phosphorus in derivation of carboalkoxy dialkylphosphonates and in the preparation of α -selenophenyl esters.



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